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LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,512	WOOLF, TOD M.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 8/29/05.

Claims 1, 2, 12-18, 24, 25, and 43-54 were canceled, and new claims 55-94 were added as requested.

Claims 55-94 are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 55-71 are indefinite because it is unclear what is intended by the phrase "between about 20-30 nucleotides in length". The claim requires the oligomer to be "between" a range of lengths. While it is possible to be "within" a given range, or "between" upper and lower limits, it is not possible to be "between" a range, because a range is a singular entity. This phrase has been interpreted as if the word "between" had been deleted, i.e. as if the double stranded oligomer was about 20-30 nucleotides in length.

Claims 72-94 are indefinite because claim 72 recites "said at least one oligomer" without antecedent basis. Also, the claims recite "said oligomer" without proper

antecedent basis, there being two antecedents, i.e. "an oligomer" and "said at least one oligomer".

Claims 76-82 are indefinite because it is unclear what are the metes and bounds of "substantially comprised of basic amino acids". It is unclear to what extent a peptide must comprise basic amino acids to be considered a member of the claimed genus because it is unclear what is meant by "substantially". The specification does not define this term in the context used in the claims, and there is no art recognized definition, so one of skill in the art cannot know the metes and bounds of the claims.

Claims 80 and 81 recite "the antennapedia protein" and "the transportan protein" without proper antecedent basis.

Claim 83 and dependents 84-94 are indefinite because it is unclear to which "oligomer" claim 83 refers.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 72-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 72 and dependents are drawn to a method of delivering an oligomer into the cytosol of a cell by contacting the cell with at least one oligomer and a fluorescently labeled transport peptide, allowing cellular uptake of the oligomer and the labeled transport peptide, and illuminating the cell with a wavelength of radiant energy that activates the fluorescent label thereby effecting release of the oligomer into the cytosol of the cell.

The claims as amended contain new matter because the specification and claims as filed did not contemplate a fluorescently labeled transport peptide. At page 6 of the response, Applicant asserts that claim 72 is supported by paragraphs 0011, 0034, 0055, 0065, 0089, 0106, 0114, and 0122. These paragraph numbers were interpreted by the Examiner to correspond to those in the published application (US 20030031655). However, a review of these passages reveals no support for a fluorescently labeled transport peptide.

The specification broadly supports methods of contacting cells with fluorescently labeled ligands, and teaches that the ligands can be oligonucleotides, or alternatively, peptides. See page 3, lines 14-23 and page 4, lines 15-18, reproduced below (corresponding to paragraphs 0011, 0012, and 0022).

This invention advances the state of the prior art by providing novel methods of enhancing the availability of ligands inside a cell. Such methods are useful both in vitro and in vivo. In one aspect, the invention pertains to a method of delivering a ligand to a cell by contacting a cell with a ligand and a fluorophore; and illuminating the cell with a light that activates the fluorophore such that the ligand is delivered to the cell.

In one embodiment, the ligand is an oligonucleotide. In another embodiment, the ligand is peptide. In another embodiment, the ligand is a fluorescent virus. In still another embodiment, the ligand is a morpholino oligonucleotide. In still another embodiment, the ligand is a sense oligonucleotide. In yet another embodiment the ligand is an antisense oligonucleotide.

In one embodiment, the ligands are fluorescent oligonucleotides. In another embodiment, the ligands are fluorescent peptides. In another embodiment, the ligands are fluorescent viruses. In one embodiment, the ligands are fluorescent morpholino oligonucleotides.

The specification as filed supports linkage of transport peptides to ligands for facilitation of cellular uptake, wherein the ligands may be peptides. See page 23, lines 17-28 (corresponding to paragraphs 0088 and 0089):

In one embodiment, ligands are modified by attaching a peptide sequence that transports the olignucleotide into a cell, referred to herein as a "transporting peptide." In one embodiment, the composition includes an olignucleotide which is complementary to a target nucleic acid molecule encoding the protein, and a covalently attached transporting peptide.

The language "transporting peptide" includes an amino acid sequence that facilitates the transport of a ligand into a cell. Exemplary peptides which facilitate the transport of the moieties to which they are linked into cells are known in the art, and include, e.g., HIV TAT transcription factor, lactoferrin, Herpes VP22 protein, and fibroblast growth factor 2 [citations omitted].

The specification also discusses the process of labeling peptides in the context of "Linking of Fluorophores to Ligands. See page 31, line 6 and the paragraph bridging pages 32 and 33 (corresponding to paragraph 0122).

These passages, and the specification as a whole, do not provide support for an interpretation of a transport peptide as a "ligand" that can be fluorescently labeled. In fact the specification distinguishes between transporting peptides and ligands, indicating that transporting peptides function to facilitate the transport of a ligand into a cell. While "ligands" may be labeled with fluorophores, there is no support in the specification for the idea that transporting peptides may be labeled with fluorophores. As a result, the specification does not contemplate a fluorescently labeled transport peptide, or a method of contacting a cell with at least one oligomer and a fluorescently labeled transport peptide. So, one of skill in the art could not conclude that Applicant was in possession of the claimed method at the time the application was filed.

It is also noted that the specification and claims as filed do not fully support the term "poly-arginine peptide" as recited in instant claim 78. This is a broad term that embraces peptides with multiple arginine residues, a few of which are disclosed in the specification, as well as arginine homopolymer peptides that are not supported by the specification. For example, the term clearly embraces e.g. a 20mer peptide composed entirely of arginine residues. There is no support for this embodiment in the specification, so claim 78 contains new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 72, 74, 75, 77, 78, and 83-87 are rejected under 35 U.S.C. 102(e) as being anticipated by Berg et al (US Patent 6,680,301, issued 1/20/04).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule from endosomes and into the cytosol. See abstract. Molecules for delivery

include DNA or RNA, including ribozymes. See column 2, lines 18-24, and claim 3 at column 23. Ribozymes are double stranded to the extent that they form intrastrand double helices. Delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38. These are considered to be "transport peptides" as recited in e.g. claim 72 because they facilitate transfer of negatively charged nucleic acids into cells by neutralizing their negative charge. Note also that instant claim 78 defines polyarginines as transport peptides. In one embodiment the photosensitizer is conjugated to the carrier, so Berg is considered to teach a fluorescently labeled transport peptide. See column 2, lines 50-54. Fluorophores include phthalocyanines and napthalocyanines. See e.g. claim 4 at column 23. The wavelength of light used will naturally vary with the photosensitizer used. Berg exemplified excitation with visible 450-490 nm light for 10 seconds. See column 13, lines 13-21.

Thus Berg anticipates the claims.

Response to Arguments

Applicant's arguments filed 8/29/05 have been fully considered as they might apply to the new ground of rejection above, but they are not persuasive.

At page 9 of the response Applicant alleges that Berg does not teach the use of a fluorescently labeled transport peptide in delivering and releasing oligomers into the cytosol of a cell. This assertion is unpersuasive for the reasons set forth above. Berg clearly taught that one may deliver oligomers to cells by complexing the oligomers with

carriers such as polylysine or polyarginine, and taught that the carriers could be conjugated with fluorophores (photosensitizers). Subsequent to cellular uptake of these complexes, irradiation of the cells leads to release of the oligonucleotides from endosomes and into the cytosol.

Applicant also opines that Berg fails to enable any method of delivering or releasing any type of oligomer into the cytosol using a fluorescently labeled transport peptide, and that one of skill in the art would have to perform undue experimentation to accomplish this based on the disclosure of Berg. This is unpersuasive because it is only an opinion and it is not supported by evidence or logic.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 55, 57, 58, 60-64, 72, 74, 75, and 83-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Fire et al (US Patent 6,506,559, issued 1/14/03).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that can be conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the

fluorescent photosensitizer, resulting in release of the molecule from endosomes and into the cytosol. See abstract. Molecules for delivery include DNA or RNA, including antisense oligonucleotides for disrupting gene expression. See column 2, lines 18-24, and claim 3 at column 23. Fluorophores include phthalocyanines and napthalocyanines. See e.g. claim 4 at column 23. Delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38. These are considered to be "transport peptides" as recited in e.g. claim 72. In one embodiment the photosensitizer is conjugated to the molecule to be delivered, or to a carrier, ensuring simultaneous contact with the cell of the photosensitizer and molecule to be delivered. See column 2, lines 50-54. The wavelength of light used varies with the excitation characteristics of the photosensitizer used. Berg exemplifies excitation with visible 450-490 nm light for 10 seconds. See column 13, lines 13-21.

Berg did not teach double stranded oligonucleotides of 20-30 nucleotides in length.

Fire taught methods of inhibiting protein expression by administration of double stranded RNAs of at least 25 nucleotides.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the double stranded oligonucleotides of Fire for the antisense oligonucleotides of Berg because Fire taught that double stranded RNA oligonucleotides had numerous advantages over antisense oligonucleotides for purposes of inhibiting protein expression. For example, Fire taught that the double

stranded oligonucleotides were more stable than antisense, and about 100-fold more effective than antisense at inhibiting protein expression (see column 3, lines 19-34 and column 5, lines 15-30). It would have been obvious to fluorescently label the polyarginine carrier protein of Berg, because Berg suggested that carrier molecules can be modified that way. See e.g. column 2, lines 61-64. Note that the instant specification at paragraph 89 defines "transporting peptide" as an amino acid sequence that facilitates the transport of a ligand into a cell. This is considered to embrace the polyarginine of Berg which facilitates transfer of negatively charged nucleic acids into cells by neutralizing their negative charge.

Claims 56 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Summerton (Biochim. et Biophys. Acta 1489: 141-158, 1999).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

While Fire also taught that the oligonucleotides may contain modified bases, the combined references did not teach morpholino modifications.

Summerton taught that morpholino modifications increase oligonucleotide resistance to nucleases. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention use morpholino oligonucleosides in the RNAs of Fire. One would have been motivated to do so in order to increase the resistance of the oligonucleotides to extracellular nucleases that might prevent delivery of intact oligonucleotides to cells.

Claims 59 and 76-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Flower et al (US Patent 6,443,976, issued 9/2/02).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm. Pertinent to claims 77 and 78, Berg taught that delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38.

These references did not teach the use of fluorescein.

Flower taught that radiation absorbing dyes such as fluorescein, phthalocyanines, and porphyrins were used to treat tumors in photodynamic therapies. Flower taught that these dyes functioned when contacted by excitatory light that caused the formation of singlet oxygen that subsequently damaged membrane components in close proximity to the dye. See detailed description paragraph 4. This principle is also disclosed by Berg at column 1, lines 34-53, and column 6, lines 1-43.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use fluorescein as a photosensitizer in the invention of Berg because Flower teaches that fluorescein functions similarly to the fluorescent activators of Berg, i.e. by producing singlet oxygen that damages membrane components in close proximity to the fluor. As such, fluorescein is a functional equivalent of the flours of Berg. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Because Berg teaches that the photosensitizer may be conjugated to the oligonucleotide delivery complex, it follows that the photosensitizer will localize to the endosomes with the oligonucleotide complex. So, one would have a reasonable expectation that the fluorescein would function to degrade the endosomes when contacted with excitatory light.

Thus the invention as a whole was prima facie obvious.

Claims 65 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Parker al (US Patent 4,541,438, issued 9/17/85).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach a flexible endoscopic light source.

Parker taught an endoscopic light source capable of delivering excitatory wavelengths of light for tetraphenylporphine sulfonates. See Figs. 4 and 5; and column 5, lines 33-44; and claims 22 and 30.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the endoscopic light source of Parker in the invention of Berg as modified by Fire because Berg taught that any light source capable of emitting the appropriate wavelength light could be used. See column 7, lines 9 and 10. As such, Berg considered all such light sources to be equivalent. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized

equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claims 66-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Pandey (US Patent 5,002,962).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

Although Berg taught that fluorophores could be conjugated to oligonucleotides and carriers, Berg was silent as to the nature of the conjugation. It is fair to interpret conjugation broadly as encompassing both covalent and non-covalent means since these are both widely known in the art. Thus, Berg taught a genus embracing the instantly claimed species, but did not explicitly teach the claimed species.

MPEP 2144.08 indicates that an obviousness rejection may be appropriate in such instances, and directs the Examiner to, as always, a) consider the scope and contents of the prior art, b) ascertain the differences between in the prior art and the clams at issue, c) determine the level of skill in the pertinent art, and d) evaluate evidence of secondary considerations. Steps a) and b) are carried out above. The level of skill in the pertinent art is evidenced by Pandey. The teachings of Pandey make it evident that it was routine in the art at the time of filing to conjugate photosensitizers to other molecules by covalent means. See column 9, lines 20-31.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention, absent secondary considerations to the contrary, to covalently conjugate the photosensitizers of Berg to either oligonucleotides or carriers. One would have been motivated to conjugate to the oligonucleotides to ensure that the oligonucleotide and photosensitizer arrived in the same cell, covalent bonds being generally more stable than non-covalent conjugation means.

Thus the invention as a whole was prima facie obvious.

Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Pandey (US Patent 5,002,962) and Parker al (US Patent 4,541,438, issued 9/17/85).

The teachings of Berg, Fire, and Pandey are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a covalently conjugated fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach a flexible endoscopic light source.

Parker taught an endoscopic light source capable of delivering excitatory wavelengths of light for tetraphenylporphine sulfonates. See Figs. 4 and 5; and column 5, lines 33-44; and claims 22 and 30.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the endoscopic light source of Parker in the invention of Berg as modified by Fire because Berg taught that any light source capable of emitting the appropriate wavelength light could be used, and because Berg taught the use of tetraphenylporphine sulfonate fluorophores. See column 6, lines 44-49, and column 7, lines 9 and 10. As such, Berg considered all such light sources to be equivalent. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on

its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claims 79, 80, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Flower et al (US Patent 6,443,976) and Baetge et al (US Patent 6,451,601)

The teachings of Berg, Fire, and Flower are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a conjugated fluorescein fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm. Berg also taught that delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38.

These references did not teach SEQ ID NO: 2, antennapedia protein, or VP22.

Baetge taught that polylysine, antennapedia, TAT, and VP22 functioned similarly in that they facilitated translocation of attached molecules across membranes.

It would have been obvious to one of ordinary skill in the art at he time of the invention to substitute the antennapedia or VP22 proteins of Baetge for the polylysine of Berg because Baetge taught that these peptides functioned as membrane translocation sequences. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case it would have been obvious to use either VP22 or antennapedia instead of polylysine because the prior art recognized that these peptides all performed a similar function. Although Baetge does not explicitly discloses SEQ ID NO: 2, this disclosure is considered to be inherent because the instant specification states that this sequence is a fragment of antennapedia. Absent evidence to the contrary, it is comprised by the antennapedia protein of Baetge.

Claims 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Flower et al (US Patent 6,443,976), Baetge et al (US

Patent 6,451,601), and Rosenecker et al (US Published Application 20030125242, published 7/3/2003).

The teachings of Berg, Fire, Flower, and Baetge are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA, a conjugated fluorescein fluorophore, and a delivery peptide such as polylysine, polyarginine, antennapedia, TAT, or VP22, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm. Berg also taught that delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38.

These references did not teach transportan protein or SEQ ID NO: 3.

Rosenecker taught that HIV-TAT, Antennapedia, and Transportan were functionally equivalent for the purpose of transferring molecules into cells. See Summary of Invention paragraph 11.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the transportan peptide of Rosenecker for the antennapedia, VP22, or TAT of Baetge, because Rosenecker taught that HIV-TAT, Antennapedia, and Transportan were functionally equivalent. Although Rosenecker does not explicitly discloses SEQ ID NO: 3, this disclosure is considered to be inherent because the instant specification states that this sequence is a fragment of antennapedia. Absent evidence to the contrary, it is comprised by the antennapedia protein of Rosenecker.

Thus the invention as a whole was prima facie obvious.

Claims 89-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Priest (US Patent 5,391,723).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore conjugated to a carrier molecule such as polylysine or polyarginine, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach an oligomer covalently linked to a fluorescently labeled transport peptide.

Priest taught the use of pH-sensitive covalent linkers to attach double stranded oligonucleotides to targeting proteins for delivery to cells. See abstract, and claim 1 at column 18.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the linkers of Priest to covalently conjugate the oligonucleotides of Fire to the polylysine or polyarginine carrier of Berg. Covalent linkage would ensure complex formation between the oligonucleotide and the carrier, and the linkers are designed to degrade in lower pH environments such as endosomes, thereby releasing

the nucleic acids from the carriers. See Priest at column 7, lines 24-36. One would have been motivated to attach a fluorescent photoactivator to the targeting protein, because Berg suggests that carrier molecules can be modified that way. See e.g. column 2, lines 61-64.

Thus the invention as a whole was prima facie obvious.

Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Priest (US Patent 5,391,723) and Parker al (US Patent 4,541,438, issued 9/17/85).

The teachings of Berg, Fire, and Priest are summarized directly above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a covalently conjugated, fluorescently labeled transport protein, allowing uptake of the RNA and the fluorescent transport protein into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach a flexible endoscopic light source.

Parker taught an endoscopic light source capable of delivering excitatory wavelengths of light for tetraphenylporphine sulfonates. See Figs. 4 and 5; and column 5, lines 33-44; and claims 22 and 30.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the endoscopic light source of Parker in the invention of Berg as modified by Fire because Berg taught that any light source capable of emitting the appropriate wavelength light could be used, and because Berg taught the use of tetraphenylporphine sulfonate fluorophores. See column 6, lines 44-49, and column 7, lines 9 and 10. As such, Berg considered all such light sources to be equivalent. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 8/29/05 have been fully considered as they might apply to the new ground of rejection above, but they are not persuasive.

Applicant asserts repeatedly at pages 11-15 that Berg does not teach or suggest a method of delivering an oligomer into the cytosol of a cell. This is false. In fact, Berg

performs a working example in which an oligomer is complexed with polylysine, delivered to a cell, the cell is treated with a fluorophore, and the oligonucleotide is released into the cytosol. See column 13, lines 8-29.

Applicant asserts repeatedly at pages 11-15 that Berg does not teach or suggest the use of a fluorescently labeled transport peptide in delivering and releasing oligomers into the cytosol of a cell. This assertion is unpersuasive for the reasons set forth above. Berg clearly taught that one may deliver oligomers to cells by complexing the oligomers with carriers such as polylysine or polyarginine, and taught that the carriers could be conjugated with fluorophores (photosensitizers). Subsequent to cellular uptake of these complexes, irradiation of the cells leads to release of the oligonucleotides from endosomes and into the cytosol.

With regard to claims 72-94, Applicant argues at page 11 that the combination of Berg and Priest fails to render obvious oligomers of 20-30 nucleotides. This is unpersuasive because this limitation is not found in claims 72-94.

Applicant asserts at page 11 that the Priest and Berg references cannot be combined with a reasonable expectation of success, and that there is no motivation to combine them. This is unpersuasive because Applicant has presented no evidence or logic to indicate that there is no reasonable expectation of success, and Applicant has not addressed the stated motivation for combining the references, i.e. the advantage of ensuring complex formation between a carrier and the oligomer until the low pH environment of endosomes is encountered.

Applicant asserts at page 13 that the Flower and Berg references cannot be combined with a reasonable expectation of success, and that there is no motivation to combine them. This is unpersuasive because Applicant has presented no evidence or logic to indicate that there is no reasonable expectation of success. Regarding the motivation to combine the references, Flower taught that fluorescein functions similarly to the fluorescent activators of Berg, i.e. by producing singlet oxygen that damages membrane components in close proximity to the fluor. As such, fluorescein is a functional equivalent of the flours of Berg. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Applicant argues at pages 15 and 16 that the Berg and Rosenecker references fail to teach an oligomer of 20-30 nucleotides. This argument does not apply to the current rejection citing these references, because that rejection is applied to claims 79-82 which do not require any oligomer of 20-30 nucleotides. Applicant also asserts at page 16 that the Rosenecker and Berg references cannot be combined with a reasonable expectation of success, and that there is no motivation to combine them. This is unpersuasive because Applicant has presented no evidence or logic to indicate that there is no reasonable expectation of success in the combination. Regarding the motivation to combine the references, Baetge taught that polylysine, antennapedia,

TAT, and VP22 functioned similarly in that they facilitated translocation of attached molecules across membranes, and Rosenecker taught that HIV-TAT, Antennapedia, and Transportan were also functionally equivalent. It follows that Antennapedia and Transportan are art recognized equivalents of polylysine in that they function to facilitate delivery of nucleic acids to cells. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

For these reasons, Applicant's arguments are not persuasive regarding the new grounds of rejection set forth above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Richard Schnizer, Ph.D.